510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k112781

B. Purpose for Submission:

The xTAG® Respiratory Viral Panel (RVP) (K063765) has been modified to improve the detection of Influenza A subtype H3 strains that were in circulation in the 2010-2011 Influenza season.

C. Measurand:

Respiratory specimen virus nucleic acid (RNA or DNA) target sequences. Viruses targeted have been associated with respiratory infections in adults and/or children.
Viral types and subtypes:
Influenza A, Influenza A H1, Influenza A H3, Influenza B, Respiratory Syncytial Virus Type A, Respiratory Syncytial Virus Type B, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Human Metapneumovirus, Rhinovirus, Adenovirus

D. Type of Test:

A multiplexed nucleic acid test for the qualitative detection and identification of multiple respiratory pathogen nucleic acids in nasopharyngeal swabs.

E. Applicant:

Luminex Molecular Diagnostics, Inc.

F. Proprietary and Established Names

xTAG® Respiratory Viral Panel (RVP)
Common Name: Respiratory Viral Panel (RVP) Multiplex Nucleic Acid Detection Assay

G. Regulatory Information:

1. Regulation section:
   21 CFR 866.3980 - Respiratory viral panel multiplex nucleic acid assay
2. Classification:
   Class II
3. Product code:
   OCC, OEM, OEP, NSU, JJH
4. Panel:
   Microbiology (83)

H. Intended Use:

1. Intended use:

The xTAG® Respiratory Viral Panel (RVP) is a qualitative nucleic acid multiplex test intended for the simultaneous detection and identification of multiple respiratory virus nucleic acids in nasopharyngeal swabs from individuals suspected of respiratory tract infections. The following virus types and subtypes are identified using RVP: Influenza A, Influenza B, Respiratory Syncytial Virus subtype A, Respiratory Syncytial Virus subtype B, Parainfluenza 1, Parainfluenza 2, and Parainfluenza 3 virus, Human Metapneumovirus, Rhinovirus, and Adenovirus. The detection and identification of specific viral nucleic acids from individuals exhibiting signs and symptoms of respiratory infection aids in the diagnosis of respiratory viral infection if used in conjunction with other clinical and laboratory findings.

xTAG® RVP can also differentiate the hemagglutinin (HA) gene of some Influenza A subtypes H1 and H3 strains. Differentiation of Influenza A HA subtypes is based on both a positive result for the Influenza A matrix gene and an accompanying positive result for the Influenza A HA subtype H1 (circulating prior to the emergence of 2009 H1N1 pdm) or Influenza A HA subtype H3. This device cannot differentiate the Influenza A HA subtype 2009 H1N1 pdm by design, and may not be able to differentiate potential newly emerging Influenza A HA subtypes.

Positive results do not rule out bacterial infection, or co-infection with other viruses. The agent detected may not be the definite cause of disease. The use of additional laboratory testing (e.g. bacterial culture, immunofluorescence, radiography) and clinical presentation must be taken into consideration in order to obtain the final diagnosis of respiratory viral infection.

Negative results do not preclude respiratory virus infection and should not be used as the sole basis for diagnosis, treatment or other patient management decisions.

The RVP assay cannot adequately detect Adenovirus species C, or serotypes 7a and 41. It is recommended that specimens found to be negative for Adenovirus after examination using RVP be confirmed by an alternate method (e.g., FDA cleared molecular test or cell culture). The RVP primers for detection of rhinovirus cross-react with enterovirus. A rhinovirus reactive result should be confirmed by an alternate method (e.g. cell culture).

Performance characteristics for Influenza A virus were established when Influenza A HA subtype H3, subtype H1 (prior to the emergence of 2009 H1N1 pdm), and when subtype 2009 H1N1 pdm were the predominant Influenza A in circulation. When other Influenza A viruses are emerging, performance characteristics may vary.

If infections with a novel Influenza A virus is suspected based on current clinical and epidemiological screening criteria recommended by public health authorities, specimens should be collected with appropriate infection control precautions for

novel virulent Influenza viruses and sent to a state or local health department for testing. Viral culture should not be attempted in these cases unless a BSL 3+ facility is available to receive and culture specimens.

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Luminex® Instrument (100 IS and 200 systems) with IS or xPONENT software

I. Device Description:

See k063765

The modified xTAG RVP assays contains the primers identical to the predicate device with the addition of a new Human Influenza A subtype H3 reverse primer sequence. The concentration of the Influenza A H3 forward primers was doubled in order to balance the added reverse primer.

Materials Provided

See k063765

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Luminex Molecular Diagnostics, xTAG® Respiratory Viral Panel (RVP)
   Common Name: Respiratory Viral Panel (RVP) Multiplex Nucleic Acid Detection Assay

2. Predicate 510(k) number(s):
   See k063765

3. Comparison with predicate:

Features	(Modified) Luminex RVP	Luminex RVP
510(k)	k112781	k063765
Regulation	866.3980	866.3980
Product Code	OCC, OEM, OEP, NSU, JJH	OCC, OEM, OEP
Device Class	Class II	Class II
Analytes Detected	Direct and differential qualitative detection of	Direct and differential qualitative detection of

Features	(Modified) Luminex RVP	Luminex RVP
	influenza types A and B, RSV types A and B, Parainfluenza types 1, 2 and 3, Human Metapneumovirus Adenovirus and Rhinovirus viral nucleic acids.	influenza types A and B, RSV types A and B, Parainfluenza types 1, 2 and 3, Human Metapneumovirus, Adenovirus and Rhinovirus viral nucleic acids.
Technology/Detection	RT-PCR Detection: Amplified products are coupled to microspheres and detected using spectrofluorometric analysis.	RT-PCR Detection: Amplified products are coupled to microspheres and detected using spectrofluorometric analysis.
Specimen Types	NP swabs	NP swabs
Nucleic Acid Isolation	NucliSENS® miniMAG extraction Kit (bioMerieux) NucliSENS® EasyMAG extraction Kit (bioMerieux) QIAamp® MiniElute® Virus Spin Kit (Qiagen)	NucliSENS® miniMAG extraction Kit (bioMerieux) NucliSENS® EasyMAG extraction Kit (bioMerieux) QIAamp® MiniElute® Virus Spin Kit (Qiagen)
Instrument /Assay Platform	Luminex 100 or 200	Luminex 100 or 200
Assay Controls	Bacteriophage lambda positive control and *E. coli* MS2 phage Internal Control –ancillary reagents not provided	Bacteriophage lambda positive control and *E. coli* MS2 phage Internal Control –ancillary reagents not provided

K. Standard/Guidance Document referenced (if applicable):
See k063765

L. Test Principle:
See k063765

Reporting Influenza A Results

- Report negative test results for Influenza A as "Influenza A Matrix gene target not detected, and hemagglutinin gene targets not detected". It is recommended that specimens found to be negative after examination using a respiratory viral panel nucleic acid detection assay be confirmed by an alternative method. Negative results do not preclude respiratory virus infection and should not be used as the sole basis for diagnosis, treatment or other patient management decisions."

- Report positive test results as "Influenza A positive, and (*where applicable*)

hemagglutinin gene target (*specify hemagglutinin target detected, e.g. H1 (prior to circulation of Influenza A 2009 H1N1pdm), or H3*).

NOTE: After the 2010-2011 season, when seasonal H1N1 has not been in circulation (following the emergency of 2009 H1N1pdm in 2009-2010), a positive RVP result for an Influenza A H1 should be verified using epidemiological information available through influenza surveillance programs.

- Positive for type (i.e., Influenza A), and negative or equivocal for hemagglutinin (HA) subtype. In the event that RVP positively identifies the Influenza A matrix gene target but fails to identify an HA gene target, this requires follow up. This result can be indicative of a device or user error, a known Influenza A HA subtype in circulation that the RVP can not differentiate by design (such as Influenza A HA subtype 2009 H1N1 pdm), or a novel Influenza A HA subtype. The end user should follow up with further testing and use the following algorithm:

  a. To rule out device or user error, retest the sample with RVP from the extraction step with external controls for these analytes. Run sample extract in duplicate. In the case where the re-test on both replicates does not yield a positive HA subtype result and external controls are properly typed, further follow-up is required.

  b. If a known Influenza A HA subtype is suspected and can not be differentiated by the assay (such as Influenza A HA subtype 2009 H1N1 pdm), the laboratory should test the sample with an alternative method to identify specific Influenza subtypes when required to definitively characterize Influenza A infections. If the sample still can not be characterized by the alternative method, that necessitates immediate notification of the appropriate local, state, or federal public health authorities to determine the necessary measures for verification of results.

- A "No Call" due to an equivocal or invalid result, should not be reported but re-tested as per recommendations. The re-test result should be considered the final RVP result for that analyte.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   See k063765

   xTAG® RVP was modified to improve reactivity to influenza A/H3 strains. No differences between the modified and the original xTAG® RVP were observed in cross-reactivity and analytical reactivity studies.

a. Detection limits:

See k063765

xTAG® RVP was modified to improve reactivity to influenza A/H3 strains. The limits of detection (LoDs) of all the analytes for the modified RVP assay were identical to the original RVP assay, except for the influenza A/H3 analyte. The modified RVP demonstrated increased analytical sensitivity detecting the hemagglutinin gene of certain influenza A/H3 strains when compared to the original device.

Table 1.Summary of Comparison of Limit of Detection (LoD) for Influenza A/H3

Strain ID Influenza A/H3	Analyte	Modified xTAG® RVP		Original xTAG® RVP	
		$TCID_{50}$/mL (at estimated LoD)	Average MFI from 22 replicates at LoD	$TCID_{50}$/mL (at estimated LoD)	Average MFI from 22 replicates at LoD
Flu A/Victoria/3/75	Flu A Matrix	0.4768	1806.84	0.4768	1776.05
	Flu A H3	0.4768	974.36	7.629	1219.64
Flu A/Perth/16/2009	Flu A Matrix	0.1347	1225.16	0.5388*	2796.07
	Flu A H3	0.1347	706.39	8.621	1441.16

* This LoD level was achieved with 22 of 22 replicates making the correct influenza A matrix POS call. At 0.1347 $TCID_{50}$/mL (one dilution level below 0.5388 $TCID_{50}$/mL), 18 of 22 replicates made the correct influenza A matrix POS call with the original xTAG RVP. The remaining 4 replicates displayed MFI values of 226, 295, 249, and 219, just below the cut-off value of 300, thus generating "No Call" results for Influenza A matrix.

2. Comparison studies:

Clinical Comparison Results

xTAG® RVP was modified to improve reactivity to influenza A/H3 strains and performance was evaluated by comparing the modified assay to the original RVP assay testing retrospective left-over clinical samples (nasopharyngeal swabs) collected from 14 clinical sites in the United States and Canada, primarily from the 2010-2011 influenza season.

All Influenza A matrix positive samples from either the original or modified xTAG® RVP were bi-directionally sequenced for influenza A subtype H3. In total, 158 influenza A positive samples by either the original or the modified xTAG® RVP were sequenced first using alternate primers outside of the kit primer binding region. All negative results with the first primer set were then re-sequenced using additional sequencing primers also outside the kit primer binding region. In addition, samples with discordant calls between the original and modified device were sequenced for the analyte(s) in question.

Positive agreement and negative agreement for each analyte were evaluated between the original and modified xTAG RVP devices (see Table 2).

Table 2. Clinical Comparison of Modified xTAG® RVP as compared to Original xTAG® RVP)

Analyte	Positive Percent Agreement (PPA)	Confidence Interval	Negative Percent Agreement (NPA)	Confidence Interval
Influenza A	98.09% (154/157)	94.52% - 99.60%	99.06% (210/212)	96.63% - 99.89%
Influenza A H1	100% (4/4)	39.76% - 100.00%*	100% (365/365)	98.99% - 100.00%
Influenza A H3	100% (80/80)	95.49% – 100.00%	85.47% (247/289)	80.87% – 89.32%
Influenza B	100% (30/30)	88.43% - 100.00%	100% (339/339)	98.92% - 100.00%
RSV A	100% (23/23)	85.18% - 100.00%	99.71% (345/346)	98.40% - 99.99%
RSV B	96.30% (26/27)	81.03% - 99.91%	100% (342/342)	98.93% - 100.00%
Parainfluenza 1	100% (6/6)	54.07% - 100.00%*	99.72% (362/363)	98.47% - 99.99%
Parainfluenza 2	100% (8/8)	63.06% - 100.00%	99.72% (360/361)	98.47% - 99.99%
Parainfluenza 3	100% (24/24)	85.75% - 100.00%	100% (345/345)	98.94% - 100.00%
hMPV	96.43% (27/28)	81.65% - 99.91%	100% (341/341)	98.92% - 100.00%
Rhinovirus	92.16% (47/51)	81.12% - 97.82%	99.69% (317/318)	98.26% - 99.99%
Adenovirus	100% (5/5)	47.82% - 100.00%*	100% (364/364)	98.99% - 100.00%

* Testing was performed on 6 or fewer positive samples for these analytes.

3. Clinical studies:

   Clinical performance characteristics of the RVP Assay were established during a prospective study at three U.S. clinical laboratories and a retrospective study at one U.S. site during the 2005-2006 respiratory virus season. Please refer to previously FDA-cleared 510(k) Premarket Notification, k063765 for additional information.

4. Clinical cut-off**:** N/A

5. Expected values/Reference range:

   See k063765

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.